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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,904	BUTLIN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/7/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 18-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15 and 16* is/are allowed.

6)☒ Claim(s) *18-39* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 15-16, 18-39 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

1. Claims 15 and 16 define over the prior art of record and are therefore allowed.

Objections/Rejections Withdrawn

2. WithdrawnClaim Rejections - 35 USC § 112: The rejection of claims 31-32 under 35 USC 112, second paragraph for reciting relative term: "give rise to a similar indication" , in light of the fact that the term "similar" has been amended to be the term "identical" and has been distinguished from the term "discernibly different".

3. ***Withdrawn Claim Objections*** Claims 24, 36 and 37 are objected to because of the following informalities: Claim 24 does not end in a period, but a comma; the claim should be amended to be a complete sentence that ends in a period. Claims 36 and 37 recite terms in italics "*reagent*" and "*zone*"; what this means is unclear. The italics should be removed. In light of the claim amendments obviating these objections.

4. Claims 35-36 and 37 rejected under the second paragraph of 35 U.S.C. 112 for reciting terms that lack antecedent basis in a prior claim from which they depend has been obviated by amending the claims to provide antecedent basis for the limitations recited in the claims.

5. Claims 18-19 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Anobile et al (1998) in light of the amendment of claim 18 to recite the first and second assays to use first and second antibody pairs.

6. Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Ulloa-Aguirre, Alfredo et al (1995), in light of the amendment of claim 18 to recite the first and second assays to use first and second antibody pairs.

Response to Arguments/ Rejections/Objections Maintained

7. Applicant's arguments filed August 7, 2006 have been fully considered but they are not persuasive.

8. ***Claims Objection***: Applicant traverses the objection to claim 22 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous

claim, Applicant asserts the antibody pairs of claim 21 "may recognize different regions of the same antigen".

9. It is the position of the Claim 21 does not require the antibody pairs to bind to different regions of the same antigen, but even if the antibodies did bind to different regions of the subunits of FSH, this does not preclude the antibodies from measuring total FSH in the sample. The members of each antibody pair of claim 21 are required to be different members and to bind to the alpha and beta subunits of FSH. In light of the knowledge in the art (see Rose et al above) that the alpha subunit presents at least 5 epitopes and the beta subunit presents at least two epitopes. Clearly two pair of antibodies with differing binding specificities would and could bind to different epitopes presented in the alpha and beta subunits and detect total FSH.

10. Additionally, the Examiner agrees that antibodies with differing binding specificities may bind to the same antigen, and in this instance, different epitopes presented by FSH, in different ways but still detect Total FSH in the sample because total FSH is accomplished through detecting the combination of FSH alpha and beta chains through binding of one antibody to the alpha subunit and another antibody of the antibody pair to the beta subunit.

11. Applicant further traverses the objection to claim 22, by stating that " the application shows two specific antibodies, both of which were induced against the combination of alpha and beta chains, which have different binding specificity."

12. It is the position of the examiner that Applicant's traversal is not commensurate in scope with the instantly claimed invention of claims 21-22. Claim 21 does not claim any specific antibodies but generically claims the utilization of two antibody pairs in sandwich immunoassay formats to detect FSH, the FSH comprising both the alpha and beta subunits, the antibodies

being directed against the alpha and beta chains of FSH. The first and second antibody pairs of claim 21 bind to the alpha and beta peptide chains would detect total FSH as does the antibody pair of claim 22 detect Total FSH. Claim 22 is not further limiting of claim 21 as now claimed because the binding specificities for the two pair of antibodies as claimed in claim 21, requires the first pair of antibodies to be different from the second pair of antibodies but both must bind to the "combined alpha and beta chains". Stating that first two antibodies are different from the second two antibodies does not define anything about their binding specificities other than they each bind to the alpha and beta subunits differently. Therefore, the two pairs of antibodies, while evidencing different binding specificities for the same FSH gonadotropin alpha and beta subunits, the two antibody pairs would bind to total FSH as total FSH is determined by measuring binding of the entire FSH molecule that contains both the alpha and beta chains in the claimed sandwich-format assay in claim 20, from which clams 21 and 22 depend.

13. It is the position of the Examiner that the phrase "combined alpha and beta chains of FSH" was defined by Applicant's own Specification at page 5 lines 32-33 that states "the alpha and beta peptide chains are the same in all FSH forms". The differences in FSH forms are defined in the instant Specification to be based upon "glycoforms (Instant Specification, page 5, line 25)". Claim 21 does not recite the term "glycoforms", nor "glycoprotein", but recites the phrase "alpha and beta chains of FSH" which are taught to be the same in all FSH based upon the two peptide chains (see page 5, line 18). The claims have been read in light of the definitions provided by the Instant Specification which permit the immunoassay of different peptide epitopes present on the alpha and beta subunits, as well as different carbohydrate epitopes on the alpha and beta subunits. Both antibody pairs that bind to both the alpha and beta subunits of

FSH would measure Total FSH. No structural differences in the antibodies, nor any specific epitopes have been so claimed to distinguish the antibody pairs in such a way that they would not bind total FSH. If the one or both of the antibody pairs of claim 21 is not to detect Total FSH, then the pairs should be so claimed based upon original descriptive support provided in the instant Specification. The second pair of antibodies that binds to the alpha and beta chains of FSH will also bind and detect total FSH, while binding with differing binding specificities, to a different combination of peptide epitopes.

14. The alpha and beta chains present a plurality of peptide and conformational epitopes. Rose et al (2000) reviews FSH epitopes (see page 12, col. 2, paragraph 2) and states that the main antigenic epitopes of the subunits of FSH have been identified using a panel of 181 monoclonal antibodies. The alpha subunit was found to present at least 5 epitopes and two on the beta subunit, and an additional two which were conformational epitopes based upon the dimer-formed between the alpha-beta subunit. Bousfield et al (page 4, Figure 1, "hFSH") show human FSH to present both glycosylated and unglycosylated regions to which antibodies may bind. Glycosylation free regions of the peptide chains would present differing epitopes to which each of the first and second antibody pairs would bind. Therefore, the two antibody pairs set forth in claim 21, which bind to the alpha and beta chains of hFSH, would both measure total FSH in the sample.

15. If Applicant intends one of the pairs of antibodies recited in claim 21 not to bind total FSH based upon binding both the alpha and beta subunits, then this embodiment is not clearly set forth in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself.

Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed .

16. The rejection is maintained for reasons of record and responses set forth above. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed.

17. ***Rejection Maintained, Claim Rejections - 35 USC § 102:*** Claims 18, 26, 31,38 rejected under 35 U.S.C. 102(b) as being anticipated by Alfthan et al (1996) is traversed on the grounds that Alfthan et al do not teach or suggest two assays using a different antibody pairs directed against a different form of the gonadatropin.

18. It is the position of the examiner that Alfthan et al (1996) disclose a method that comprises the steps of:

Obtaining a gonadotropin containing sample from a female individual (see section 7.3.2page 111, and page 112, serum samples, each individual sample is represented by the single data indicator "o".)

Performing contemporaneous first and second assays on the sample obtain in step (a) (see page 2, "hCGβ" just below hCG serum graph and hCG upper left frame under serum), the antibody pair for hCG differs from that of hCG-β because hCG contains both an alpha and beta subunit while hCG-β only contains the beta subunit (definitions, see page 107, col. 2, paragraphs 2-3) The hCG immunometric assay method comprises one antibody to the alpha subunit and one antibody to the beta subunit (see page 109, col. 2, paragraph 2). The hCG-β sandwich immunometric assay is based upon two antibodies directed to the hCG-β beta subunit (see page

109, col. 2, paragraphs 3-4 and (page 111, section 7.3.2). Therefore Alfthan et al disclose first and second antibody pairs that bind to two different forms of hCG and based upon comparison between these values, menopausal status can be determined. The rejection is maintained for reasons of record and responses set forth herein.

19. The rejection of claims 18, 26, 31-32 and 38 under 35 U.S.C. 102(e) as being anticipated by Birken et al (US Pat. 6,521,416 B1) is traversed on the grounds that Birken et al do not teach or suggest two assays using a different antibody pairs directed against a different form of the gonadatropin.

It is the position of the examiner that Birken et al disclose the instantly claimed invention directed to a method of testing a human female individual to determine menopausal status, the method comprising two assay that employ tow antibody pairs directed to different forms of the gonadotropin (see col. 8, Figures 15 A-C, two assays, the first being for hLH concentration (figure 15C) and the second being a different form of hLHBcf which is dependent upon menopausal status (see Figure 15 A (perimenopausal, col. 8, lines 26-43), the antibody being specific for a protein portion and a carbohydrate moiety (see col. 10, lines 33-35; see sandwich format assays hLHBcf: col. 4, lines 40-5151; hLH: two different IRMAs (see col. 6, lines 62-63), IRMA are sandwich assays; Figure 8; also col. 9, lines 50-55; assay results were discernibly different from each other (see Figure 17 A-B and col. 8, lines 45-52 "no pattern match"; "typical postmenopausal concentrations of the hLHBcf"; col. 13, lines 50-56 differences in hLH and hLHBcf (increased 6X-7X); the detection/determining was from the formation of color (see col. 9, lines 64-67 "enzyme, dye" produce color indications in assays).

Birken et al still anticipates the instantly claimed invention as now claimed.

20. The rejection of claim 39 under 35 U.S.C. 102(b)as being anticipated by O'Daly et al (US Pat. 5,391,272) is traversed on the grounds that Applicant has amended claim 39 to require the forms to be the same gonadotropin.

It is the position of the examiner that the claimed article, comprises a device that is configured to have three components.

The first configuration is to **receive a sample** (O'Daly et al discloses a device configured to receive a sample means for combining the signals produced (spectrophotometric assay (see col. 20, lines 37-38 and claims 20-47 (electrode surface)).

The second configuration is to "provide a **first signal**" (O'Daly et al disclose a devise with a first signal producing means that is a signal producing means that is gonadotropin-responsive(see col. 20, lines 25-59)).

The third configuration is to "provide a **second signal**" (O'Daly et al disclose a devise that also comprises a second signal producing means that is a signal producing means that is gonadotropin-responsive(see col. 19, lines 25-68, and col. 20, lines 1-23). O'Day anticipates the instantly claimed invention as now claimed because the article of O'Daly comprises a de vice with the claimed three configurations that are a sample receiving, and first and second signal producing means. (colloidal gold adsorbed anti-FSH together with an "enzyme/antibody conjugate(see claims 29-30))

21. Rejection Maintained ***Claim Rejections - 35 USC § 103. The rejection of*** claims (method)18-23, 24, 26-28, 29, 38; (device) 33-37 and 39 under 35 U.S.C. 103(a) as being unpatentable over Berger (1988) in view of EP 0736771 A1 (1995) is traversed on the grounds

that Berger does not disclose the various FSH forms detected by the disclosed antibody pairs and are not correlated with menopausal status.

22. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "the various FSH forms detected") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

23. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

24. Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

It is also the position of the examiner that Berger sought to determine the detailed antigenic topography of hFSH based upon a large number of monoclonal antibodies to elucidate, and characterize hFSH forms associated with elevated or decreased levels of FSH associated with metabolic dysfunctions (see Berger page 2351, col. 2, p. 2-3 and col. 1, paragraph 2).

25. Applicant asserts that EP 0736771 does not teach or suggest how the FSH forms disclosed in Berger would correlate to menopausal status.

26. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., how the FSH forms disclosed in Berger would correlate with menopausal status) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims do not recite any specific forms, just different forms, and EP0736771 teaches how to correlate the determination of hFSH with menopausal status. It is also the position of the examiner that Berger teaches changes in gonadal axis result in elevated or decreased FSH levels are known (see page 2351, col. 1, last paragraph) and characterizes the antigenic epitopes with a panel of antibody pairs which define combinations of reagents for mapping/characterizing and determining the presence or absence of hFSH associated with changes in hFSH levels in a biological samples and EP 0736771 Bartoli teaches hFSH, to be a clinical marker for diagnosing a woman with menopause (see title, figure, abstract) and Bartoli provides teaching, guidance for the evaluation of biological samples for determining specific changes in hFSH levels associated with menopausal status

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Berger et al with the biological samples of Bartoli because both references measure hFSH in a biological sample with sandwich format immunoassays and teach the importance of measuring hFSH as a marker for gonadal

dysfunctions, and Bartoli teaches and shows hFSH to be a marker for determining the menopausal status of a female individual.

As a showing of unexpected results has not been submitted the claimed invention is still obviated by the combination of Berger et al in view of Bartoli (EP0736771), for reasons of record and responses set forth herein.

27. The rejection of claims 25 and 30 under 35 U.S.C. 103(a) as being unpatentable over Berger in view of Bartoli, as applied to claims 18-23, 24, 26-28, 29, 38; (device) 33-37 and 39 above, and further in view of Dullien (US Pat. 6,174,665) is traversed on the grounds that Dullien does not remedy the deficiency of Berger in view of Bartoli and asserts that the combination of references does not teach or suggest the claimed invention.

28. It is the position of the examiner that Berger in view of Bartoli do teach a method of determining the menopausal status of a female individual, the sample evaluated is not from a female undergoing a course of hormone replacement therapy (HRT).

Dullien teaches and shows the measurement of hFSH in a sample (see col. 4, lines 13-17) obtained from female human individual undergoing hormone replacement therapy (see title, abstract, col. 4, lines 57-59) in an analogous art for the purpose of monitoring hormone replacement therapy for effectiveness in alleviating symptoms associated with menopausal status (see Dullien col. 3, lines 9-20).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Berger in view of Bartoli with the sample of Dullien because Berger, Bartoli and Dullien all measure the presence and amount of hFSH in a human sample, and Dullien teaches the importance of measuring hFSH in a sample obtained

from a human female undergoing a course of hormone replacement therapy (HRT) because Dullien teaches the importance of aggressively monitoring HRT therapy through assaying hFSH to insure the dosage of HRT administered is within the optimal range, the optimal range being that range which will provide for the greatest effectiveness in releaving undesired symptoms associated with menopausal status, and if the dosage of HRT prescribed deviates from the optimal range a modified treatment dose can be determined(See Dullien, col. 4, lines 37-45).

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of assaying a human female individual undergoing HRT for the presence of hFSH to determine menopausal status in view of the guidance and teaching provided by Berger, Bartoli in view of Dullien because Dullien teaches the optimal ranges for FSH in blood, urine and saliva in a female individual undergoing hormone replacement therapy in order to assess menopausal status (see Dullien, col. 4, lines 55-63; and col. 3, lines 9-15).

A showing of unexpected results has not been submitted therefore, Berger, Bartoli in view of Dullien obviate the instantly claimed invention as now claimed.

Conclusion

29. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vgp
November 8, 2006

MARK NAVARRO
PRIMARY EXAMINER